UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/672,399	09/25/2003	Linda Pilarski	A894635US	1833

37047 7590 05/19/2005

GOWLING LAFLEUR HENDERSON LLP
SUITE 1400, 700 2ND ST. SW
CALGARY, AB T2P 4V5
CANADA

EXAMINER	
YAO, LEI	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/672,399	PILARSKI ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4-7-05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-105* is/are pending in the application.

4a) Of the above claim(s) *18-20,24-26,35-37,40-44,51-87 and 91-105* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,21, 23,27-28, 30-34,38-41,45-50 and 88-90* is/are rejected.

7)☒ Claim(s) *22 and 29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: *Exhibit A*.

B

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I with species election of HAS1Va in the reply filed on 4/7/05 is acknowledged.

Applicants argue that the restriction is improper because examiner has incorrectly stated that "the DNA of group II can be used to express protein as opposed to being used to hybridize two a gene transcript'. Applicants also argue "applicant submits that DNA is not capable of being used to "express protein" rather DNA may be used to generate a RNA template from which ribosomes may assembly polypeptides/proteins, "generation of RNA from a DNA template is not a materially different process from that described for the DNA of Group II; in that the processes involved in replication and ensuring fidelity pf replication involve hybridization of individual ribonucleotides to the DNA template prior to ligation to the nascent RNA strand with fidelity processes assessing the quality and character of hybridized polyribonucleotides".

These have been considered, but not found persuasive. Invention group II claims products of DNA and a diagnosis kit, whereas invention group I is involved in the process of using the DNA for detection of expression of HAS1Va by hybridization. According to MPEP ¶ 806.05(h) A product and a process of using the product can be shown to be distinct inventions if either or both of the following can be shown: (A) the process of using as claimed can be practiced with another materially different product; or (B) the product as claimed can be used in a materially different process. It is known in the art that DNA provides genomic information, which is widely used beyond than detection of a gene expression by hybridization, such as to produce protein in biological research and therapy for medicine. Although applicant state, "DNA is not capable of being used to express protein rather DNA may be used to generate a RNA template from which ribosomes may assembly polypeptides/proteins", the argument is not different from MPEP ¶ 806.05(h)'s statement as above since "generate a RNA template" and further "assembly polypeptides/proteins" is a process of making a protein using the same genetic code of DNA

and is still different usage than hybridization for detecting the expression of HAS1Va in invention I. In addition, as MPEP ¶ 806.05(h) (B) state" the product as claimed can be used in a materially different process". Generation of RNA from a DNA template **IS** a materially different process from what described for the DNA of Group II as hybridization to detect the expression of HAS1Va. For these reasons, the group I and II are patentablely distinct inventions and the restriction requirement is deemed to be proper and is adhered to. The requirement is therefore made **FINAL.**

Claims 1-50 and 88-90 are pending. Claims 18-20, 24-26, 35-37, and 42-44, withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Claims 1-17, 21-23, 27-34, 38-41, 45-50, and 88-90 will be examined on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Drawn to Written Description

Claims 1-10 and 28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-10 are broadly drawn to a method to detect or characterize expression HAS isoenzyme variants in a cell population comprising contacting "**an agent"** capable of selectively binding to HAS isoenzyme variant genomic products. Because the claims do not limit "an agent" in terms of particular conserved structural attributes, no metes and bounds can be determined for the term "an agent". Thus, one skill in the art cannot envision the detailed chemical structure of the encompassed "an agent".

Claim 28 is broadly drawn to a method to detect expression of HAS1Va comprising detection of "**single nucleotide polymorphism**" of the HAS1Va gene. Because the claim does not limit "single nucleotide polymorphism" in terms of specific nucleic acid alternation or particular location of the HAS1Va gene no metes and bounds can be determined for the term "single nucleotide polymorphism" of the HAS1Va gene. Thus, one skill in the art cannot envision the location or alternation of the encompassed "single nucleotide polymorphism".

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

In this case, claims 1-10, encompass "an agent" capable of selectively binding to HAS isoenzyme variant genomic products. The specification teaches "the agent include, but not be limited to, an antibody, or antibody fragment" (page 25, lien 2-3). The specification further teaches "the method comprising contacting an agent that binds to HAS1Va nucleotide so as to form a complex" (page 22, line 7-8). However, the specification does not teach the structural characteristic of any other agent that can bind to HAS1Va genomic product so as to form a complex other than an antibody, antibody fragment and nucleotides. It is known in the art that nucleotides binding agent could be a molecules structurally different from nucleotides. It is also known in the art that a protein binding agent could be a molecules structurally different from an antibody. Disclosed antibody and nucleotide do not anticipate the claimed genus because the genus includes molecules, which differ widely in structural attributes from nucleotides or antibody. In the absence of sufficient recitation of distinguishing structural characteristics, the specification does not provide adequate written description of the claimed genus. Therefore, the written description is not commensurate in scope with the claims, which read on "an agent" capable of selectively binding to HAS isoenzyme variant genomic products. One of skill in the art would reasonably conclude that applicant was not in possession of the claimed genus.

In this case, claim 28 encompasses genus of "single nucleotide polymorphism". However, the specification only provide one "single nucleotide polymorphism" at conversion of base-pair 924 from cytosine to a thymidine residue of SED ID NO: 1. No any other kind of "single nucleotide polymorphism", such as addition, deletion, or mutation at other position of the HAS1Va gene is descripted in the specification. The disclosed "single nucleotide polymorphism" at conversion of base-pair 924 from cytosine to a thymidine" does not anticipate the claimed genus because the genus includes molecules, which differ widely in structural attributes from the polymorphism at conversion of base-pair 924 from cytosine to a thymidine. In the absence of sufficient recitation of distinguishing structural characteristics, the specification does not provide adequate written description of the claimed genus. Therefore, the written description is not commensurate in scope with the claim, which reads on "single nucleotide polymorphism". One of skill in the art would reasonably conclude that applicant was not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Therefore, for "an agent", only nucleic acid and antibody but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph and for "single nucleotide polymorphism", only ONE single nucleotide polymorphism at conversion of base-pair 924 from cytosine to a thymidine,

but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Drawn to Enablement:

Claims 30-31, 38-41, and 45-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims are drawn to a method to detect "**susceptibility to disease**" comprising characterizing of HAS isoenzyme variant expression and susceptibility results from genetic instability.

The factor considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re wands,* 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

To satisfy the requirement of 112, 1st paragraph, it is necessary that the specification provides an enabling disclosure of how to make and use a claimed invention. The method objective of claims is detecting the disease susceptibility by characterization or detection of the expression of HAS1Va and polymorphism of the gene. Thus, it would be expected that one of skill in the art would be able to use the method to detect susceptibility to the disease according to the level of HAS1Va without undue experimentation by using the claimed method. Instant specification states that the invention provides a method to diagnose the susceptibility of a cell or cell population to disease through characterization of the expression of HAS isoenzyme or isoenzyme variants. The instant specification also states that the invention provides another aspect, for the use of nucleic acid probes or primers enabling characterization

of HAS isoenzyme or isoenzyme variant expression in a cell or cell population as a determinant for the susceptibility of a cell or cell population to disease (page 16, line lien 7-13). The specification teaches that overexpression of HAS1Va occurs in the multiple myeloma (MM) cells (page 63, example 4). The specification also teaches that aberrant splicing of HAS1 gene in MM could impact the patient survival (page 69, example 8). However, the specification provides little or no guidance for the correlation between the expression of HAS1Va in an individual who has not yet developed a disease and susceptibility to the disease. The specification provides not evidence or data of the relationship between the developmental process of MM and level of HAS1Va. The specification provides no teaching or any working example for how to determine the susceptibility to disease by detecting the expression of HAS1Va variants in an individual who has not yet developed a disease. The state of art recognizes that detecting disease susceptibility would require the detection of the HAS1Va before the onset of the disease. The specification teaches that HASV1Va is elevated as a result of the disease. There is no objective evidence or art of record to support the allegation that the elevated level of HAS1Va precedes the disease state, rather than results from the disease state. Without knowing if the elevated expression of HSA1Va precedes a disease state, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the claimed method.

Therefore, in view of the lack of guidance and working example in the specification and in view of the unpredictability in the art of combination cancer therapy evidenced by Long et al and Goss et al. One skill in the art would not expect the success on detection susceptibility to disease by characterizing of the expression of HAS1Va. One skill in the art would be forced into undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-8, 17, 21, 23, 30, 32-34 and 49-50 are rejected under 35 U.S.C. 102(b) as being anticipated by Calabro et al., (Blood, vol 100, page 2578-2585, 2002).

Claim 1 is drawn to a method to detect expression of hyaluronena synthase (HAS) isoenzyme variants in a cell or cell population comprising contacting an agent capable of selectively binding to HAS isoenzyme variant genomic products. Claims 2-8 embody the claim 3, wherein the genomic product is nucleotide, mRNA. Claims 21 and 23 are drawn to a method of detect expression of HAS1. Claims 30-34 are drawn to a method to detect a disease comprising characterizing HAS expression in a cell population comprising bone marrow plasma cells. Claims 49-50 are drawn to method to determine the likelihood of poor outcome in a human suffering from multiple myeloma comprising characterizing HAS expression in a cell population comprising bone marrow plasma cells.

Calabro et al., disclose a method to detect HAS isoenzyme variant genomic product, specifically mRNA expression in the bone marrow plasma cells from multiple myeloma patient bone marrow aspirates and from the myeloma cell line (PAGE 2579, column 1, paragraph 1). Calabro et al., disclose that Multiple myeloma is a malignancy characterized by the accumulation of malignant plasma cells within the bone marrow (page 2578, column 1, paragraph 2). Calabro et al., further disclose that HAS1 mRNA is expressed predominantly in the myeloma bone marrow plasma cells from multiple myeloma patient compared with normal bone marrow cells (figure 1. page 2582, column 1, paragraph 2).

2. Claims 11-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Venter et al., (US Patent NO: 6812339).

Venter et al., disclose antibodies that recognize a protein (sequence ID 11530, available at website, http://seqdata.uspto.gov), which is 99.4 identical to HAS1Va amino acid sequence at residues 1-310 as evidenced by attached sequence search (exhibit A). Venter et al., disclose that the antibodies selectively bind to the variant proteins as well as the fragments. Venter et al., also disclose that antibodies can be used to quantitatively or qualitatively detect the variant proteins or variant peptides (column 13, line 34-38). Venter et al., also disclose that the antibody is facilitated by coupling to detectable substance, for instance, fluorescent material, radioactive material, horseradish peroxidase as a colorimetric material (column 14, line 20-26). Venter et al., also disclose that labeled antibodies can use to detect variant protein in biological sample for determining the amount of variant proteins and comparing the amount of variant proteins in the sample (column 37, line 3-9). Venter et al., further disclose "Antibodies are preferably prepared from regions or discrete fragments of the variant protein containing a variant amino acid. Antibodies can be prepared from any region of the variant peptide as described herein, provided that the region contains a variant amino acid encoded by a nonsynonymous nucleotide substitution at single nucleotide polymorphisms position (SNP) disclosed by the present invention" (column 13, line 66 to column 14, line 5).

It is noted that in Venter et al.'s, Patent, sequence of SEQ ID 11530 comprises more than 80% amino acid sequence, which is more than 99% identical to the N-terminal domain of HAS1Va. It would be reasonable to conclude that the polyclonal antiserum included antibodies, which specifically bound to the HAS1Va isoenzyme variant polypeptides. It would also be reasonable to conclude that the antibodies, which were prepared to bind to the specific positions in the variant proteins of Venter et al., would bind to one of the instant HAS1Va variants to the exclusion of the others. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 1-10, 17, 21, 23, 27, 30, 32-34 and 49-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Calabro et al., (Blood, vol100, page 2578-2585, 2002) in view of Kopf-Sill (US Patent NO: 6303343).

Claims 1-8, 17, 21, 23, 30, 32-34 and 49-50 are set forth above. Claims 9 and 10 embody the claim 1,wherein the complex is detected using a fluorescent label and performed using a microfluidic device. Claim 27 embodies the claim 21, wherein the process is performed using a microfluidic device.

Calabro et al., teach a method detecting expression of HAS isoenzyme variant genomic product, specifically mRNA expression in the bone marrow plasma cells from multiple myeloma patient, as set forth above.

Calabro et al., do not teach that detection of HAS expression by PCR uses fluorescent labeling or that the process is performed by microfluidic device.

Kopf-Sill teaches a method of performing a PCR reaction in microfluidic devices. Kopf-Sill first teaches that fluorescently labeled nucleotide can be incorporated into a nucleic acid during PCR reaction (column 18, line 54-57). Kopf-Sill further teaches a detail method to perform the PCR in a microfluidic device system (column 8-28).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teaching of Colabro et al., on the detecting expression of HAS1 genomic product with the teaching of Kopf-Sill on the performing PCR reaction by a microfluidic device system. One of ordinary skill in the art would have been motivated to use the teachings of Colabro et al., and the teaching of Kopf-Sill to detect expression of HAS1 genomic product by fluorescent labeled PCR

reaction performed by a microfluidic device system because Colabro et al., have shown a method of detecting expression of HAS1 genomic product in a cell population by contacting an nucleotide to the HAS1 genomic product and Kopf-Sill has shown that detecting the PCR product, the complex formed between nucleotides, can be performed in a microfluidic device. One of skill in the art at the time of invention would have a reasonable expectation of success in detecting expression of HAS1 genomic product by fluorescent labeled PCR reaction performed using a microfluidic device system.

2. Claims 88 and 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raje et al., (Curr Treat Options Oncol, vol 1, page 73-82, 2002) in view of Calabro et al., (Blood, vol 100, page 2578-2585, 2002).

Claims 88-89 are drawn to method to monitor malignant cells in a human comprising detection of HAS in a cell population comprising multiple myeloma.

Raje et al., teach a method of treating MM and monitoring the remission rate in the treated MM patients (all paper).

Raje et al do not teach the monitoring of MM pateints by the measurment of the expression of HAS.

Calabro et al., teach that Multiple Myeloma (MM) is a malignancy characterized by the accumulation of malignant plasma cells within the bone marrow. Calabro et al., also teach that expressions of HAS isoenzyme variant genomic product (mRNA) in the bone marrow plasma cells from MM patients are higher than the normal bone marrow plasma, as set forth above.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to monitor patients having undergone treatment for MM by monitoring the expression of HAS in said patients. One of ordinary skill in the art would have been motivated to use the teachings of Calabro et al., and Raje et al., to monitor the malignant cells in a MM patient by detecting the expression of HAS isoenzyme because Calabro et al., have shown a method of detecting expression of HAS isoenzyme and role of HAS in MM condition and because Raje et al., have shown the treatment of MM

and monitoring the treated MM patients after treatment. One of skill in the art at the time of invention would have a reasonable expectation of success in monitoring the malignant cells in MM patients by detecting the level of HAS isoenzyme.

3. Claims 88 and 90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adamia et al., (Seminars in Oncology, Vol 30, page 165-168) in view of Desikan et al., (Biodrugs, vol 6, page 201-7, 2002).

Claims 88 and 90 are drawn to method to monitor malignant cells in a human comprising detection of HAS in a cell population comprising Waldenstrom's Macroglomulemia.

Adamia et al., teach that aberrant expression of HAS1 is coupled with Waldenstrom's Macroglomulemia (WM). Adamia et al., teach expression profile of HAS1 in the bone marrow cells and peripheral blood of WM patients (page 166, table 1). Adamia et al., also teach that HAS gene is overexpressed in WM (page 166, column 1, paragraph 1).

Adamia et al., do not teach a method of monitoring malignant cells in human suffering from WM.

Desikan et al., teach that WM is a rare B cell malignancy characterized by marrow and tissue infiltration (page 202, column 1, paragraph 1). Desikan et al., teach methods of WM therapy and observation of response to the treatment (page 202-203).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teaching of Adamia et al., on overexpression of HAS isoenzyme in the bone marrow and peripheral blood cells from WM patient, with the teaching of Desikan et al., on method of treating WM and observation of response to the treatment in the WM patients. One of ordinary skill in the art would have been motivated to use the teachings of Adamia et al., and Desikan et al., to monitor the malignant cells in a WM patient by detecting the expression of HAS isoenzyme because Adamia et al have shown a method of detecting expression of HAS isoenzyme and role of HAS in WM condition and because Desikan et.al., have shown the treatment of WM and observation of the response to the treatment in WM patients. One of skill in the art at the time of invention would have a reasonable

expectation of success in monitoring the malignant cells in WM patients by detecting the level of HAS isoenzyme.

Claim Objections

Claims 22 and 29 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-4.30pm Monday to Friday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Dowining for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao, Ph.D.
Examiner
Art Unit 1642

LY

KAREN A. CANELLA PH.D
PRIMARY EXAMINER

```
Db         61 AFLSAHLVAQSLFAYLEHRRVAAAARGPLDAATARSVALTISAYQEDPAYLRQCLASARA 120

Qy        121 LLYPRARLRVLMVVDGNRAEDLYMVDMFREVFADEDPATYVWDGNYHQPWEPAAAGAVGA 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 LLYPRARLRVLMVVDGNRAEDLYMVDMFREVFADEDPATYVWDGNYHQPWEPAAAGAVGA 180

Qy        181 GAYREVEAEDPGRLAVEALVRTRRCVCVAQRWGGKREVMYTAFKALGDSVDYVQVCDSDT 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 GAYREVEAEDPGRLAVEALVRTRRCVCVAQRWGGKREVMYTAFKALGDSVDYVQVCDSDT 240

Qy        241 RLDPMALLELVRVLDEDPRVGAVGGDVRILNPLDSWVSFLSSLRYWVAFNVERACQSYFH 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 RLDPMALLELVRVLDEDPRVGAVGGDVRILNPLDSWVSFLSSLRYWVAFNVERACQSYFH 300

Qy        301 CVSCISGSLG 310
              |||||||  ||
Db        301 CVSCISGPLG 310


RESULT 2
US-09-949-016-11530
; Sequence 11530, Application US/09949016
; Patent No. 6812339
; GENERAL INFORMATION:
;  APPLICANT: VENTER, J. Craig et al.
;  TITLE OF INVENTION: POLYMORPHISMS IN KNOWN GENES ASSOCIATED
;  TITLE OF INVENTION:  WITH HUMAN DISEASE, METHODS OF DETECTION AND USES THEREOF
;  FILE REFERENCE: CL001307
;  CURRENT APPLICATION NUMBER: US/09/949,016
;  CURRENT FILING DATE:  2000-04-14
;  PRIOR APPLICATION NUMBER: 60/241,755
;  PRIOR FILING DATE: 2000-10-20
;  PRIOR APPLICATION NUMBER: 60/237,768
;  PRIOR FILING DATE: 2000-10-03
;  PRIOR APPLICATION NUMBER: 60/231,498
;  PRIOR FILING DATE: 2000-09-08
;  NUMBER OF SEQ ID NOS: 207012
;  SOFTWARE: FastSEQ for Windows Version 4.0
; SEQ ID NO 11530
;   LENGTH: 589
;   TYPE: PRT
;   ORGANISM: Human
US-09-949-016-11530

  Query Match             80.2%;  Score 1594;  DB 4;  Length 589;
  Best Local Similarity   99.4%;  Pred. No. 9.5e-164;
  Matches  308;  Conservative    0;  Mismatches    2;  Indels    0;  Gaps    0;

Qy          1 MRQQDAPKPTPAARRCSGLARRVLTIAFALLILGLMTWAYAAGVPLASDRYGLLAFGLYG 60
              ||||||||||||| |||||||||||||||||||||||||||||||||||||||||||||
Db         12 MRQQDAPKPTPAACRCSGLARRVLTIAFALLILGLMTWAYAAGVPLASDRYGLLAFGLYG 71

Qy         61 AFLSAHLVAQSLFAYLEHRRVAAAARGPLDAATARSVALTISAYQEDPAYLRQCLASARA 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         72 AFLSAHLVAQSLFAYLEHRRVAAAARGPLDAATARSVALTISAYQEDPAYLRQCLASARA 131

Qy        121 LLYPRARLRVLMVVDGNRAEDLYMVDMFREVFADEDPATYVWDGNYHQPWEPAAAGAVGA 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        132 LLYPRARLRVLMVVDGNRAEDLYMVDMFREVFADEDPATYVWDGNYHQPWEPAAAGAVGA 191

Qy        181 GAYREVEAEDPGRLAVEALVRTRRCVCVAQRWGGKREVMYTAFKALGDSVDYVQVCDSDT 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        192 GAYREVEAEDPGRLAVEALVRTRRCVCVAQRWGGKREVMYTAFKALGDSVDYVQVCDSDT 251

Qy        241 RLDPMALLELVRVLDEDPRVGAVGGDVRILNPLDSWVSFLSSLRYWVAFNVERACQSYFH 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        252 RLDPMALLELVRVLDEDPRVGAVGGDVRILNPLDSWVSFLSSLRYWVAFNVERACQSYFH 311

Qy        301 CVSCISGSLG 310
              |||||||  ||
Db        312 CVSCISGPLG 321


RESULT 3
US-08-675-499A-3
; Sequence 3, Application US/08675499A
; Patent No. 6492150
;  GENERAL INFORMATION:
;    APPLICANT:  McDonald, J. A.
;    APPLICANT:  Spicer, A. P.
;    APPLICANT:  Augustin, M. L.
;    TITLE OF INVENTION:  GENE ENCODING HYALURONAN
;    TITLE OF INVENTION:  SYNTHASE
;    NUMBER OF SEQUENCES:  32
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Schwegman, Lundberg, Woessner & Kluth, P.A.
;      STREET:  P.O. Box 2938
;      CITY:  Minneapolis
;      STATE:  MN
;      COUNTRY:  USA
;      ZIP:  55402
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Diskette
;      COMPUTER:  IBM Compatible
;      OPERATING SYSTEM:  DOS
;      SOFTWARE:  FastSEQ Version 2.0
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/675,499A
;      FILING DATE:  03-JUL-1996
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:
;      FILING DATE:
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  Woessner, Warren D
;      REGISTRATION NUMBER:  30,440
;      REFERENCE/DOCKET NUMBER:  150.170US1
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  612-359-3260
;      TELEFAX:  612-359-3263
;      TELEX:
;  INFORMATION FOR SEQ ID NO:  3:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  583 amino acids
;      TYPE:  amino acid
;      STRANDEDNESS:  single
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  protein
US-08-675-499A-3

  Query Match             75.9%;  Score 1509;  DB 4;  Length 583;
  Best Local Similarity   93.9%;  Pred. No. 1.6e-154;
  Matches  295;  Conservative    2;  Mismatches   11;  Indels    6;  Gaps    2;

Qy          3 QQDAPKPTPAARRCSGLARRVLTIAFALLILGLMTWAYAAGVPLASDRYGLLAFGLYGAF 62
              :|| |||: ||| ||||||| ||| ||||||||||||||||||||||||||||||||||
Db          2 RQDMPKPSEAARCCSGLARRALTIIFALLILGLMTWAYAAGVPLASDRYGLLAFGLYGAF 61

Qy         63 LSAHLVAQSLFAYLEHRRVAAAAR-----GPLDAATARSVALTISAYQEDPAYLRQCLAS 117
              |||||||||||||||||||||||     |||||||||||||||||||||||||||||| |
Db         62 LSAHLVAQSLFAYLEHRRVAAAARRSLAKGPLDAATARSVALTISAYQEDPAYLRQCLTS 121

Qy        118 ARALLYPRARLRVLMVVDGNRAEDLYMVDMFREVFADEDPATYVWDGNYHQPWEPA-AAG 176
              |||||||  ||||||||||||||||||||||||||||||||||||||||||||| | |
Db        122 ARALLYPHTRLRVLMVVDGNRAEDLYMVDMFREVFADEDPATYVWDGNYHQPWEPAEATG 181

Qy        177 AVGAGAYREVEAEDPGRLAVEALVRTRRCVCVAQRWGGKREVMYTAFKALGDSVDYVQVC 236
              ||| ||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        182 AVGEGAYREVEAEDPGRLAVEALVRTRRCVCVAQRWGGKREVMYTAFKALGDSVDYVQVC 241

Qy        237 DSDTRLDPMALLELVRVLDEDPRVGAVGGDVRILNPLDSWVSFLSSLRYWVAFNVERACQ 296
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        242 DSDTRLDPMALLELVRVLDEDPRVGAVGGDVRILNPLDSWVSFLSSLRYWVAFNVERACQ 301

Qy        297 SYFHCVSCISGSLG 310
              ||||||||||| ||
```

Exhibit A